CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-251

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 15, 1997

Edmund A. Egan, MD
President
ONY, Inc.
1576 Sweet Home Road
Amherst, NY 14228

Dear Dr. Egan:

This correspondence responds to your letter of March 14, 1997, submitted under the dispute resolution provisions of 21 CFR 314.103. In that letter you requested resolution of whether Infasurf is the "same" drug as Survanta within the meaning of the Orphan Drug Act (ODA) exclusivity regulations found at 21 CFR 316.3(b)(13).

Since our receipt of that letter, several communications have occurred between you and the Center for Drug Evaluation and Research (CDER), which have also been considered in preparing this response:

May 7, 1997: Tentative approval letter to NDA 20-521 (Infasurf)
May 13, 1997: Your letter to Dr. Bilstad, Director, Office of Drug Evaluation II
May 28, 1997: Your FAX to the Division of Pulmonary Drug Products providing preliminary results of a study designed to demonstrate that Infasurf is not the "same" drug as Survanta
June 9, 1997: Your letter to Mr. Morrison, CDER Ombudsman
June 11, 1997: Presentation (transcribed) by you, your consultants and attorneys to Drs. Woodcock, Lumpkin and FDA staff members

We have carefully reviewed these materials and have conducted internal meetings with appropriate agency staff to deliberate the issues you raised. For the reasons outlined briefly below, we have concluded that, in the context of the ODA and its corresponding regulations, Infasurf and Survanta are the "same" drug, and Infasurf has not been shown to be clinically superior to Survanta or to make a major contribution to patient care as defined in the regulations. Hence, we affirm the tentative nature of the approval of NDA 20-521, which precludes marketing until July 1, 1998, when the ODA exclusivity granted to Survanta expires.

Although we have concluded that you have not demonstrated that Infasurf is clinically superior to Survanta or that it makes a major contribution to patient care not currently provided by Survanta, we understand and are sympathetic to your concern that there may be a population of neonatal patients with Respiratory Distress Syndrome (RDS) who fail to respond to Survanta but who may respond to Infasurf.

The Federal Food, Drug and Cosmetic Act permits great flexibility in the conditions under which new drugs are studied. We believe that your assertion that Infasurf is clinically superior to Survanta in unresponsive neonates, although currently not supported by clinical data, should be pursued and that the efficacy of Infasurf for patients who fail Survanta ought to be explored. The Center stands ready to work with you to expeditiously devise an appropriate mechanism to study Infasurf in clinical settings that may conclusively answer the questions regarding its effectiveness relative to Survanta. We strongly encourage you to contact the Division of Pulmonary Drug Products to discuss the design of such a study pending full marketing of Infasurf next year.

Our conclusions regarding the specific arguments made in your appeal have been grouped into the following general areas:

Composition and Activity Differences Between Infasurf and Survanta:

The agency's decision in 1991 that approval of Survanta was not blocked by Exosurf's orphan drug exclusivity does not compel the same conclusion with respect to Infasurf and Survanta. Exosurf is a mixture of three synthetic active ingredients, with no undefined components. Two of the three active components in Exosurf (cetyl alcohol and tyloxapol) are not present in Survanta. In contrast, Survanta is a complex mixture of lipids and proteins derived from bovine lungs. Exosurf and Survanta differ markedly in composition and have only one component in common (DPPC).

On the other hand, both Infasurf and Survanta are complex mixtures of lipids and proteins derived from bovine lungs. They are very similar in their composition, with both products containing all six of the "active" components (DPPC, PC, SP-B, SP-C, palmitic acid and tripalmitin) that were identified in your presentation of June 11 in addition to a number of other identified components that may contribute to their activity. Although Infasurf and Survanta contain differing quantities of these six components, they are both effective surfactants, and you have not demonstrated that such quantitative differences are relevant to the clinical activity of the products. Individual components of Survanta may be important to its overall activity, but it is difficult to ascertain accurately the relative contribution of each one. Thus, in the absence of more data, all components must be considered to contribute to the activity of these products.

Further, we do not agree with your assertion, based on the statements contained in the description section of the Survanta package insert, that Survanta could contain no protein at all, in contrast to Infasurf, which contains specified amounts of total protein and SP-B. Based upon our knowledge of the Survanta NDA, we are

confident that all batches of Survanta released for marketing do contain protein. Further, data from your own laboratories have consistently demonstrated that marketed batches of Survanta contain protein and SP-B.

Clinical Superiority of Infasurf over Survanta:

We have conducted a thorough review of the Infasurf versus Survanta comparative trial in your NDA and have concluded that the data do not support a claim of clinical superiority for Infasurf. Infasurf's superiority over Survanta was not demonstrated for any of the recognized clinically relevant endpoints (e.g., mortality, incidence of RDS, incidence of bronchopulmonary dysplasia, air leaks, etc.). In fact, in the prophylaxis arm of the trial mortality was actually lower for neonates treated with Survanta than those treated with Infasurf. The small differences observed between the products in physiologic endpoints, such as FiO_2 and MAP, are of unknown clinical significance and are not adequate to support a claim of clinical superiority. Likewise, your post hoc subset analysis of patients with "severe, persistent RDS," while raising a hypothesis for future study, cannot be the basis of a finding of clinical superiority. Further, the small differences observed between Infasurf and Survanta in frequency of dosing, percent of patients requiring a full course of treatment, and the like are not an adequate basis to support a finding that Infasurf provides a major contribution to patient care not currently provided by Survanta.

We also disagree with your assertion that the "Acute Clinical Effects" paragraph in the Clinical Pharmacology section of the Infasurf labeling suggests clinical superiority. The cited paragraph describes the acute clinical effects observed in infants following treatment with Infasurf compared to baseline, not a comparison of Infasurf-treated versus Survanta-treated infants. Similar language is found in Survanta and Exosurf labeling as well.

Interpretation of the Orphan Drug Exclusivity Regulations:

We agree that the orphan drug regulations do not identify a specific regulatory mechanism for determining "sameness" in the case of Infasurf and Survanta, drugs consisting of mixtures of large and small molecules. However, we believe that the relationship between Infasurf and Survanta is analogous to that described in 21 CFR 316.3(b)(13)(ii)(D). Infasurf and Survanta are closely related drug products (lung surfactants derived from bovine sources). Also, they are complex (composed of many components), partly definable (not all of the constituent molecules have been identified and quantified), and have the same therapeutic intent. Therefore, we believe Infasurf and Survanta should be considered the same from the chemical standpoint in the context of orphan drug exclusivity.

As you can appreciate, this discussion of our conclusions is not exhaustive, given the quantity of written materials and oral arguments you have provided and given our extensive review, analysis and internal discussions. However, we have enclosed a more detailed analysis prepared by the Division of Pulmonary Drug Products that was relied upon by CDER, along with other materials, in considering your appeal. We hope you find it helpful to you in understanding the basis for our decision.

In closing, we would like to express our sincere appreciation for your patience and for your professionalism while pursuing this appeal. We look forward to working with you in a continuing cooperative effort in this critical health area.

Sincerely yours,

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

Enclosure:
Memorandum dated 7/2/97 Jenkins to Woodcock, redacted for FOIA

NDA 20-521

SEP 26 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

Reference is also made to the Agency's letter dated May 24, 1996, and your submissions dated July 19 and August 13, 1996, in which you propose a plan to demonstrate that Infasurf and Survanta are not the "same drug" under Orphan Drug Regulations.

We agree with your proposal to demonstrate that Infasurf and Survanta differ in a specific active component by demonstrating both that the particular component is present and active in one surfactant and that it is either not present or present at levels that render it inactive in the other surfactant. However, we have the following comments regarding your proposal.

1. All experimental procedures and tests should be carried out in replicate on both drug products, Survanta and Infasurf, under the same experimental conditions to assure consistency and validity. Your August 13, 1996, proposal to perform experimental tests on Infasurf only, is unacceptable.

2. All methods should be properly described and validated. The choice of methods should be adequately justified to assure sufficient characterization and quantitative composition of the "modified" drug product.

3. The methods used for assessment of *in vitro* activity of the drug product preparations should include both the bubble surfactometer and excised rat lung test. If alternative methods will be used, they must be shown to be well correlated with clinical effects.

4. All tests and measurements should be conducted in a randomized and fully blinded fashion.

5. A detailed protocol of your experimental plan and your plan for analysis of the data should be submitted for review prior to the initiation of the experimental studies. The protocol should include a prespecified definition, rationale and *in vivo* data-based justification of what will be considered a meaningful difference, or lack thereof, between formulations.

Should you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-521

MAY 24 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York, 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your pending July 27, 1995 new drug application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf.

Reference is also made to the April 26, 1996 telephone conference between Dr. Larry Olanoff, Mr. Laszlo Ek, Mr. Sultan Aziz, Ms. Debbie Urquhart from Forest Laboratories, Mr. Alan Kaplan from his Washington, D.C. law office, Mr. William Ferguson and yourself from ONY, Inc., and Dr. James Bilstad from the Office of Drug Evalution II, Dr. John Jenkins, Dr. Jean Nashed, and Ms. Betty Kuzmik from this Division.

At that telephone conference, we informed you that the Agency has determined, based on the information currently available, that Infasurf and Survanta are considered the same drug from the standpoint of the Orphan Drug Regulations. The rationale supporting this decision is that, in contrast to drugs composed of small molecules to which the concept of an active moiety (21 CFR 316.3(b)(2)) applies, surfactants are a complex mixture of both large and small molecules, many of which have poorly defined specific or unique physiologic functions. As such, surfactants are most like the macromolecules in that it would be trivially easy to make minor changes in a surfactant that would leave the activity of the drug unaltered, but would create a "new drug" if the micromolecular definition of active moiety were applied. The Agency believes that the paradigm of macromolecules should be applied to surfactant drugs. 21 CFR 316.3(b)(13)(ii)(D), states that "Closely related, complex partly definable drugs with similar therapeutic intent,...would be considered the same unless the subsequent drug was shown to be clinically superior." Therefore, based on currently available data, we conclude that Infasurf and Survanta should be considered the "same drug."

As we discussed, should you wish to apply the "active moiety" concept to a particular component of surfactants, you would need to demonstrate both that the particular component is present and active in one surfactant and that it is either not present or present at levels that are inactive in the other surfactant. As discussed in the Federal Register of December 29, 1992 (57 FR 62077), different in vitro biologic activity will not normally suffice to support a claim of clinical superiority because of concern that in vitro activity may not correlate with clinical effects. As such, any in vitro or pre-clinical models used to support the activity of individual components of surfactants should be well correlated with clinical effects.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-521
HFD-570/Div File
HFD-570/Pina
HFD-570/Himmel
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/Koutsoukos
HFD-570/Wilson
HFD-570/Choi
HFD-570/Sun
HFD-570/Gillespie
HFD-570/Conner
HFD-570/Schumaker/5-21-96
HF-35/Mccormick
GCF-1/Dickinson
R/D by MHimmel
Draft letter typed by Bkuzmik/5-14-96 and 5-21-96
Reviewed by Drs. McCormick, Jenkins, Bilstad, and Ms. Dickinson/5-21-96

n:\kuzmikb\20521.let

Kuzmik

NDA 20-521

FEB 28 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your pending July 27, 1995 new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf.

We also refer to your amendments dated August 10, 22, September 26, and December 1, 1995.

To complete our review of the chemistry sections of your submission, we request the following.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Betty Kuzmik
Project Manager
(301) 827-1054

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachments A and B enclosed

cc:

Original NDA 20-521
HFD-570/Div. Files
HFD-570/CSO/Betty Kuzmik
HFD-570/JNashed
HFD-570/Pina
HFD-570/Choi
HFD-570/Gillespie
HFD-570/Koutsoukos

DISTRICT OFFICE

drafted: BK/February 21, 1996/n20521.chm
reviewed by: Cschumaker/2-21-96; Jnashed/2-23-96;
Gpoochikian/2-23-96; Mpina/2-22-96; MHimmel/2-23-96
final: SmithV 2/26/96

INFORMATION REQUEST (IR)

**APPEARS THIS WAY
ON ORIGINAL**

Kuzmik

NDA 20-521

AUG 8 1995

Ony, Inc.
c/o Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Attention: Michael M. Rosen, Ph.D.
Director of Regulatory Affairs

Dear Dr. Rosen:

We have received your new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Infasurf (calf lung surfactant extract) Intratracheal Suspension

Therapeutic Classification: Standard

Date of Resubmitted Application: July 27, 1995

Date of Receipt: July 31, 1995

Our Reference Number: NDA 20-521

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 29, 1995 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Betty Kuzmik
Consumer Safety Officer
Telephone: (301) 827-1054

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-521
HFD-155/Div. Files
HFD-80
HFD-155/CSO/Betty Kuzmik BK 8/4/95
HFD-155/Schumaker/8-2-95 8/8/95

drafted: BKuzmik/August 2, 1995/n20521.ack
Final: Vsmith 8/3/95

ACKNOWLEDGEMENT (AC)

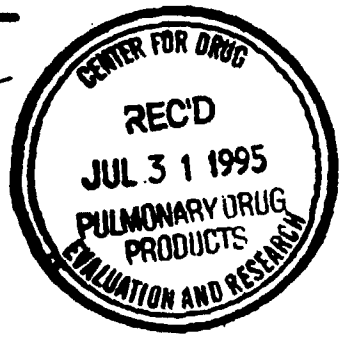
APPEARS THIS WAY
ON ORIGINAL

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

ORIGINAL

July 27, 1995

~~A(B)~~
N(RS)
DRUG AMENDMENT



John Jenkins, MD, Acting Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-155
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-521 Resubmission**
Product: **Infasurf (calf lung surfactant extract)**

Dear Dr. Jenkins,

This is a resubmission of NDA 20-521. Reference is made to your letter dated July 13, 1995 in response to the July 6, 1995 meeting between ONY, Inc, Forest Laboratories and FDA.

In response to item # 1 of that letter we are submitting the data presented at the meeting which supports the contribution of SP-B to the effect of Infasurf. In order to conform with the instructions that the data be submitted "...in a manner consistent with an NDA submission" we have prepared this information as an extension of:

Section 3.3.1
Description of the Physical and Chemical Characteristics of the Drug Substance

The data contains a substantial amount of data about the drug product and pharmacologic and physiologic activity. However, it was decided to add it into this section of the NDA because its focus is the chemical definition of the Active Moiety of Infasurf and the other surfactants.

The additional text pages have been numbered 03 0004 A through 03 0004 J and 03 0006 A. The additional references have been numbered 03 0105 (A-1) through 03 0105 (A-46). This resubmission data can be stored separately or it can be added to NDA 20-521 without affecting the pagination of the remainder of the NDA document.

We will provide comparative CMC data from an FDA inspected laboratory for the comparative analysis of SP-B using appropriately validated methods in 4-6 lots of Infasurf and Survanta by December 1, 1995. We will include the dates of testing, the batch number and the expiration date for each analysis.

In addition we will develop specifications of components of Infasurf including SP-B. Using retained vials from lots used for clinical trials we will link SP-B concentration in clinical trial lots to that in to-be-market lots. This development will proceed in parallel with the comparative testing of SP-B between Infasurf and Survanta.

Sincerely,

FOREST LABORATORIES, INC

for

Michael M. Rosen, PhD
Director of Regulatory Affairs

ONY, INC.

Edmund A. Egan, MD
President

KUZMIK

NDA 20-521

JUL 13 1995

ONY, Inc.
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Reference is made to your March 13, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract).

Further reference is made to our refuse to file (RTF) letter dated May 10, 1995, your May 18, 1995 request for a meeting to discuss the RTF letter and the July 6, 1995 meeting that took place between representatives of ONY, Inc. and FDA.

The new information that was presented at the meeting provides a theoretically valid argument that Infasurf is different from Survanta. We are willing to file your NDA if the following are included in your resubmission.

1. The data which were presented at the meeting and which support the contribution of SPB to the effect of Infasurf must be submitted in a manner consistent with an NDA submission.

2. Commit to provide comparative CMC data from an FDA inspected laboratory for the analysis of the SPB in Survanta and Infasurf by no later than 4 months after the NDA is resubmitted. Appropriately validated methods should be used to generate the requested comparative data on 4 to 6 batches of each product. The data should include the batch number and expiration of the batch tested and the date the analysis was performed.

If the determination is made that Infasurf is different from Survanta based on the above comparative data, appropriate regulatory specifications must be set for various components in Infasurf including SPB. Since SPB was not specifically assayed in the clinical lots, you must propose a plan for linking the clinical lots with the to-be-marketed lots with regard to concentration of SPB.

The application will be considered resubmitted when we have received the data requested in #1. above.

If you have any questions, please call Ms. Betty Kuzmik, Consumer Safety Officer at (301)827-1054.

Sincerely yours,

John K. Jenkins, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-521
HFD-155/Div File
HFD-155/Himmel
HFD-155/Pina
HFD-155/Poochikian
HFD-155/Ng
HFD-155/Kuzmik 7/13/95
R/D/Schumaker/7-10-95
Revised:MHimmel/7-10-95
GPoochikian/7-11-95
LNg/7-11-95
R/D init:MPina/7-11-95
c:\schumake\n20521.let
F/T by: VSmith
GENERAL CORRESPONDENCE

7/13/95

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the General Counsel

Office of the Chief Counsel
Food and Drug Administration
5600 Fishers Lane, GCF-1
Rockville, MD 20857

MEMORANDUM

Date: May 28, 1996

To: Dr. James M. Bilstad, HFD-102

From: Elizabeth Dickinson, GCF-1 EHD

Subject: Refusal to File/Orphan Exclusivity

You have asked whether the agency may refuse to file an NDA when the approval of the application will be blocked by another sponsor's exclusivity for the same drug product under the Orphan Drug provisions of the Federal Food, Drug, and Cosmetic Act.

For the reasons given below, I believe that the agency may not refuse to file an application under these circumstances.

The Orphan Drug provisions of the FFDCA provide for a grant of seven years of market exclusivity for drug products that are approved for the treatment of diseases or conditions affecting fewer than 200,000 persons in the U.S. During this period of exclusivity, FDA may not approve any other application for the same drug for the same indication. The preamble to the final regulations implementing the exclusivity portions of the Orphan Drug Act states that

> once the agency determines that approval of a drug would be temporarily barred by the exclusive marketing provisions of the Orphan Drug Act, the timing of the review will be decided on a case-by-case basis by the appropriate division... . Such decisions will be based on time and resource considerations as well as on the complexity of information to be considered.

57 Fed. Reg. 62076-77 (December 29, 1992).

Although this language apparently was intended to give the agency some flexibility in deciding when to review applications for drug products that could not be approved immediately due to orphan exclusivity, there is no corresponding provision in the regulations that provides a legal basis for refusing to file an application under these circumstances.

The Orphan Drug regulations address, among other issues, the requirements for orphan drug designation, the basis for determining whether two drug products are "the same," and the granting of Orphan Drug exclusivity. See generally 21 C.F.R. § 316. The filing of an NDA for a drug product that has obtained an orphan product designation under §316.24 is governed by the general NDA filing regulations at 21 C.F.R § 314.101; there are no filing regulations specific to orphan-designated products.

The filing regulations provide that the agency "will file" an NDA if it finds that none of the reasons in § 314.101(d) or (e) apply. None of the enumerated reasons is applicable to an NDA that could not be approved because of orphan exclusivity. Moreover, there is no general "catch-all" provision that could provide a basis for refusing to file the application under the circumstances contemplated by the preamble language. Absent such specific or general provision in the regulations, the agency may not refuse to file an NDA on the grounds that approval of the application would be barred by another sponsor's orphan exclusivity.

cc: Dr. Robert Temple, HFD-101
Linda Carter, HFD-101
Dr. John J. McCormick, ODP
Peter Vaccari, OPD

Ann Wion, GCF-1

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the General Counsel

Office of the Chief Counsel
Food and Drug Administration
5600 Fishers Lane, GCF-1
Rockville, MD 20857

MEMORANDUM

Date: March 20, 1997

To: Dr. James Bilstad, HFD-102

From: Elizabeth Dickinson, GCF-1 EHD

Subject: Tentative Approvals and Orphan Exclusivity

You have asked me whether CDER can issue a tentative approval letter for a new drug application when final approval of the application is blocked by orphan exclusivity. My conclusion is that a tentative approval letter should be used in such circumstances.

The Orphan Drug provisions of the Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360aa-360dd, provide for a grant of seven years of market exclusivity for drug products that are approved for the treatment of diseases or conditions affecting fewer than 200,000 persons in the U.S. During this period of exclusivity, FDA may not approve any other application for the same drug for the same indication.[1] Because the agency cannot refuse to file an NDA for a drug product on the grounds that another sponsor's product has orphan exclusivity,[2] the agency is now faced with a situation in which a new drug application is nearing the point at which, but for the existence of another sponsor's orphan exclusivity for the same drug for the same indication, the application would be eligible for final approval. This raises the question of what action the agency should take at the time the application is approvable but for exclusivity.

---

[1] Orphan exclusivity blocks approval of any application for the same drug for the same indication; it is the only form of exclusivity that will block an NDA for which the applicant conducted or sponsored all necessary studies (a "stand-alone" NDA). Three year exclusivity will block approval only of a 505(b)(2) or 505(j) application. Five year new chemical entity exclusivity prevents the agency from accepting a 505(b)(2) or 505(j) application during that period, but does not bar acceptance or approval of a stand-alone NDA.

[2] See my May 28, 1996, memo to you on this subject.

FDA regulations provide for issuance of a number of different types of approval-related letters. The agency can issue an approval letter, including an approval letter with a delayed effective date (a "tentative" approval) under 21 CFR § 314.105; an approvable letter under § 314.110; a not approvable letter under § 314.120; or a refusal to approve under § 314.125. The latter two options are not appropriate for the situation at issue, in that they involve a finding by the agency of one or more of the deficiencies enumerated at § 314.125. None of these deficiencies relates to an exclusivity bar to approval.

An approvable letter also is not appropriate when all that blocks approval of an application is the existence of orphan exclusivity. An approvable letter is used when substantially all of the statutory requirements are met and the agency believes it will be able to approve that application if additional material or information is submitted or certain conditions are met by the applicant. In the case of an approval blocked by exclusivity, there is nothing additional that the applicant can do to move the application toward approval; only the passage of time will remove the barrier. The regulation at § 314.110 notes that in most instances an approvable letter is a mechanism for resolving outstanding issues for drugs that are about to be approved and marketed. The regulation contemplates a short time frame for resolution of the outstanding issues identified in an approvable letter, in that there is a 10 day timeframe for an initial response to the letter.

The most appropriate action for the agency to take in the event that final approval of an NDA is blocked by orphan exclusivity is to issue a final approval with a delayed effective date, also called a "tentative" approval. The regulations state that approval letters are effective as of the date of issuance, except in the case of a 505(b)(2) application which has a delayed effective date. § 314.105. A 505(b)(2) application may have a delayed effective date due to outstanding patent issues or exclusivity. § 314.107. Although the regulations do not expressly provide for use of tentative approvals for stand-alone NDAs for which final approval is blocked by orphan exclusivity, the basis for using the tentative approval mechanism is the same in both cases: final approval is blocked by exclusivity. The Office of Generic Drugs (OGD) routinely issues these tentative approval letters under § 314.105(d) and § 314.107 when final approval of a generic drug application is blocked by a patent or by exclusivity.[3/] The use of tentative approvals in conjunction

---

[3/] The regulations also do not expressly address the use of a tentative approval letter when final approval of a 505(b)(2) application or 505(j) application is blocked by orphan exclusivity. The exclusivity referred to in § 314.107(d) and

(continued...)

with orphan exclusivity is fully consistent with the new drug approval provisions and the orphan exclusivity provisions of the statute, and with our regulations. Omission of orphan exclusivity from coverage by these regulations appears to have been an oversight.

One issue to bear in mind in using tentative approvals for NDAs where final approval is blocked by orphan exclusivity is that there could be a period of many years between the issuance of the tentative approval letter and the expiration of orphan exclusivity. The standard tentative approval letter issued by OGD requires that prior to the time the application will be eligible for final approval, the ANDA applicant must file an amendment to its application to provide, among other things, updated information related to labeling; chemistry, manufacturing and controls; and other changes in conditions tentatively approved in the ANDA. You may want to discuss with OGD any experience they have had with tentative approvals that pre-date final approval by more than a year or two, because in such cases, the agency may want to require submission of additional information prior to final approval. Because of PDUFA and review time considerations, you also may want to require that such information be submitted not more than 180 days prior to the expiration of orphan exclusivity, so that final action on the amendment can be coordinated with expiration of exclusivity.

The Office of Orphan Products Development has reviewed the question of issuing tentative approval letters for drug products where final approval is blocked by orphan exclusivity, and does not foresee any adverse impact on the orphan products program from this approach.

Please feel free to call me at 827-1126 if you have any additional questions.

cc: Robert Temple, M.D., HFD-101
Paula Botstein, M.D., HFD-103
David Feigal, M.D., HFD-104
Michael Weintraub, M.D., HFD-105
Murray Lumpkin, M.D., HFD-2
Roger Williams, M.D., HFD-3
Jane Axelrad, HFD-5
Marlene Haffner, M.D., HF-35
John McCormick, M.D., HF-35

2/(...continued)
described in § 314.108, is only that exclusivity provided under the Waxman-Hatch amendments, not orphan exclusivity. The analysis set out in this memorandum would apply as well to use of tentative approvals when final approval of a 505(b)(2) or 505(j) application is blocked by orphan exclusivity.

Doug Sporn, HFD-600
Gordon Johnston, HFD-601
Don Hare, HFD-604
Ann Wion, GCF-1
David Horowitz, GCF-1

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-521

JAN 13 1997

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

Reference is also made to the Agency's letters dated May 24 and September 26, 1996, and your submissions dated July 19, August 13, November 14, and December 24, 1996, in which you propose a plan to demonstrate that Infasurf and Survanta are not the "same drug" under Orphan Drug Regulations.

We have reviewed your November 14, 1996, version of the protocol for testing to prove that Infasurf is different from Survanta and we have found it still inadequate. It should be expanded and modified to provide an adequate amount of details about the proposed testing. The following are general comments and recommendations.

1. The same testing methods, procedures, and conditions should be applied to all Infasurf and Survanta preparations during all drug product modifications, testing, interpretation of the results, etc. Please refer to Protocol 2, (A) and (B) and to comment #1 in our letter dated September 26, 1996.

2. A detailed analysis of components of Infasurf and Survanta should be provided before and after each modification to assure that only the targeted component has been altered and that the relative proportion of the remaining components and other parameters/attributes of the drug product formulations have not been changed, as discussed during our meetings of March 20 and July 9, 1996. Also, please refer to comment #2 in our September 26, 1996, letter.

3. We recommend that the level of each "depleted" component (see p.3, Methodology A.5) be lowered significantly (at least 10 fold below the usual entry level) and the reconstitution with the "depleted" component be based on the original amount of that ingredient. Furthermore, we advise that the determination of the "activity" of each altered formulation be also supported by the initial testing study of a reasonable number of Survanta and Infasurf batches to establish base line of a given component.

4. We recommend that all drug product preparations, before and after modifications, be tested by the following:

   a. Bubble surfactometer (we recommend reporting value of surface tension with time, e.g., from 0 to 15 min); and

   b. excised rat lung test.

   A clear and comprehensive plan of data analysis, including assessment of the "activity" of each preparation that is based on the results of both tests should be provided. Please refer to comment #5 below and to comments #3 and #5 in our September 26, 1996, letter.

5. We recommend that the assessment of the "active" and "inactive" status of the Survanta and Infasurf preparations be contingent on the *in vivo* data-based justification of what is considered a meaningful difference. Please refer to comment #5 in our September 26, 1996, letter.

6. The protocol should specify the number of lots of each drug product to be tested, the number of preparations of each altered drug product to be examined, the number of assays to be repeated, etc. All results should be reported in addition to the "mean ± STD" values.

7. Sample sizes should be clearly stated and should be based on a two-sided α-level of 0.05 and 80% power.

8. While showing that the two compounds are statistically different, the methodology of testing the null hypothesis of "no difference" will suffice; however, while showing that the two compounds are equivalent, you should state what you mean by equivalence quantitatively as an interval. Hence, the statistical method will be similar to the analysis of a bio-equivalence study. The reference for this methodology is Schuirmann, Donald; "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability"; Journal of Pharmacometrics and Biopharmaceutics, Vol. 15, No. 6, 1987.

9. Please state prospectively how you plan to combine the p-values obtained from the bubble surfactometer test and the excised lung test.

10. As discussed during the telephone conference of December 9, 1996, your response to the approvable letter of July 25, 1996, is currently under review. An action letter based on our review of your submission will be sent to you within 6 months of the receipt of your submission.

11. The Division continues to believe that the data submitted in this NDA to date are inadequate to demonstrate the clinical superiority of Infasurf over Survanta. However, the Division is committed to working closely with sponsors to facilitate the drug approval process and, as we have in the past, are available to meet with you to discuss your concerns or questions regarding the Infasurf vs Survanta issue.

Should you have any questions or wish to schedule a meeting to discuss our comments on your protocol or to further discuss your contention that Infasurf is clinically superior to Survanta, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

Martin D. Hummel MD

for

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

May 13, 1997

James Bilstad, MD
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-521
Infasurf (calfactant)

Dear Dr. Bilstad:

Please refer to your May 7, 1997 letter in which you state that the review of this new drug application has been completed and that it has been concluded by the FDA that the drug is safe and effective for use as recommended in the draft physician labeling and carton and container labeling dated May 5, 1997 and May 6, 1997. Your letter requested, but did not require, specified "minor editorial changes" which you incorporated in the labeling enclosed with your May 7 letter. We are agreeable to making the changes requested.

Your letter indicates that final approval of the new drug application may not issue until July 1, 1998 "due to the orphan exclusivity granted to Ross Laboratories' product Survanta...unless you [ONY] can show that Infasurf and Survanta should not be considered the 'same drug' within the meaning of the Orphan Drug regulations, 21C.F.R. Part 316".

As you and other officials of the Agency know, ONY has taken the consistent position since NDA 20-521 was submitted that Infasurf and Survanta are not "the same drug". The "same drug" question had not been raised by FDA before that time. Since then, ONY has presented data from qualified experts of why the two are not the "same drug". The Agency has never explicitly addressed ONY's data and has never come forward with information to refute it.

As you know too, by letter dated March 14, 1997, ONY requested that FDA convene a panel of independent experts qualified to assess these two drugs, obtain the views of all interested persons, and draw a conclusion as to their same or different status. We requested that the action be completed by mid-April. We have never had a response to the March 14 letter.

While it may appear ironic, it now appears that the "same drug-different drug" question has been resolved by the contents of the FDA-revised physician labeling enclosed with your letter of May 7, 1997. The labeling itself show that Survanta and Infasurf are not "the same drug".

The first indicia is that FDA has determined that the proteins SP-B and SP-C have not been shown to be active components in Survanta but are active components of Infasurf. In its May 26, 1996 letter to ONY, the Agency declared that Infasurf was a macromolecular drug for Orphan Drug purposes under 21 C.F.R. §316.3(b)(13) because its macromolecules, proteins SP-B and SP-C, are active components. Previously, in its review of the Survanta NDA, the Agency decided that the study Abbott Laboratories submitted had not demonstrated that the proteins in Survanta were active. (Chemists Review #4, February 24, 1991 Remark #20, page 5; Review Notes (ii) to (v), page 24-26). The description of the proteins in the package inserts of Survanta and Infasurf reflect the different determinations of protein activity:

(a) Survanta has no specified amount of total protein or of SP-B, only a maximum allowable total protein, <1.0 mg/mL, which means it could have none;

(b) Infasurf has a specified amount of total protein, 0.65 mg/mL, and of SP-B, 0.26 mg/mL.

Since the Agency has not determined that protein(s) in Survanta are active, it cannot be classified as a macromolecular drug under orphan drug regulations because it is not :... a drug composed of large molecules ..." (21 C.F.R. §316.3(b)(13)(ii).) In contrast, Infasurf is a drug composed of active macromolecules by Agency determination. Therefore, ONY is immediately entitled to final approval of Infasurf under the Orphan Drug rules as applied by the Agency to the two drugs.

The second area of distinction that is apparent in the labeling of Infasurf and Survanta are the established names that have been chosen for each drug by USAN and accepted by the FDA. (See 21 U.S.C. §352(e)(1) and 21 C.F.R. §299.4.) The USAN name for Survanta is "beractant." The USAN name for Infasurf is "calfactant." If the products constituted "the same drug," they would have the same established name, in much the same manner as ANDAs carry the same established name as the reference drug upon which they rely for eligibility for approval. By reason of having different established names, Infasurf and Survanta have been officially recognized as different entities, scientifically and legally, and cannot be the same drug.

The third element in the labeling that reveals that Infasurf and Survanta are not "the same drug" is in the section of labeling headed "Infasurf versus Survanta" as set out in the FDA's version of the physician labeling. That section contains a paragraph headed "Acute Clinical Effects" which states:

> Marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (F_1O_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

The quoted sentences were composed by the FDA in substitution of more detailed wording that had been submitted earlier by ONY. While ONY believes its language is preferable to those "minor editorial changes" requested by the FDA, your letter indicates that under both the draft physician labeling presented by ONY and as revised by FDA the drug is safe and effective for use as recommended.

The above-referenced FDA drafted paragraph reveals the occurrence of "marked improvement...during the first 24 to 48 hours following initiation of Infasurf therapy" in all controlled clinical trials. The studies involved comparison of Infasurf with Survanta and with Exosurf. With Infasurf there was "significant improvement... during the first 24 to 48 hours following initiation of Infasurf therapy," when it was compared to either of the other two surfactants. (There was no placebo control in any of the studies). This paragraph reveals that even if Survanta and Infasurf were to be considered the "same drug," compositionally, at the very least the acute clinical effects of Infasurf in the time frames cited justify application of the standards of 21 C.F.R. §316(b)(3)(iii) and constitute a showing that Infasurf provides a significant therapeutic advantage and is clinically superior for purposes of Orphan Drug exclusivity. At a meeting with the Pulmonary Division on February 26, 1997, senior academic clinicians, experienced in neonatal intensive care and clinical trials of lung surfactants, expressed the view that Infasurf was clinically superior to Survanta under 21 C.F.R. §316.31(b)(iii).

Both Survanta and Infasurf are surfactants, each shown to be safe and effective in the prophylaxis and treatment of RDS in premature infants. The drugs share certain qualities but they are not "the same." The fact that FDA review has determined the proteins are active in Infasurf but not shown to be active in Survanta, that different established names have been assigned to each by USAN and accepted by the FDA, and that there are differences in patient responses which make a potentially significant contribution to the welfare of patients in the judgment of qualified experts, necessitate the conclusion that the tentative approval given Infasurf be immediately changed to a final approval. To conclude otherwise would contravene the expressed Agency intent to limit orphan drug exclusivity where there are clinical differences shown between drug products.

In additional to these arguments, we have previously submitted compositional, biophysical, philological, pharmacological and clinical data which also support our contention that Infasurf and Survanta are different drugs under the orphan drug regulations.

We request an appointment with you as soon as possible to bring this matter to an administrative resolution, the optimal solution for both the company and the Agency.

Sincerely,

Edmund A. Egan
President

cc: Drs. Lumpkin and Jenkins and Ombudsman Morrison

NDA 20-521

APR 18 1997

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

We also refer to your July 19, 1996 submission, the Agency's September 26, 1996 letter, your November 14 and December 24, 1996 submissions, the Agency's January 13, 1997 letter, your February 12, 1997 submission, and the February 26, 1997 face-to-face meeting between ONY/Forest and this Division.

Further reference is made to your March 14, 1997 submission which contains the amended protocol for an *in vitro* study which will evaluate the activity of SP-B and tripalmitin/palmitic acid in Infasurf and Survanta to demonstrate that the two surfactants are not the same drug under Orphan Drug Regulations. We also acknowledge your April 4, 1997 telephone facsimile from Dr. Richard Trout. We have reviewed these submissions and have the following general comments and recommendations.

1. With regard to the definitions of equivalence, both to Infasurf and Survanta, such a definition is most reasonably expressed as the percent of drug activity that could be lost (by the modified formulation) and still be considered equivalent to the original drug.

2. All of the statistical testing which you are planning to perform on the results from the *in vitro* studies, as well as the basis for the sample size ("n") that you have

3. The submitted protocol is somewhat ambiguous as to whether activity values for normal lung, depleted lung and original surfactant will be generated in the experiment or based on historical data. All these values should be generated as part of the experiment.

4. We note that the protocol states the specific amount of SP-C and SP-B that will be added to Infasurf and Survanta lipids. Since these modified formulations should have equivalent amounts of proteins to the original surfactant used in the experiment, the amount of proteins to be added to the lipids cannot be pre-specified. Rather, these amounts should be based on your assays of the protein content of the unmodified surfactants actually used in the experiment. The "removed" and "added" proteins should be fully characterized. Please refer to comment #2 from the Agency's September 26, 1996 and January 13, 1997 letters.

5. The protocol states that each preparation will be tested on 8 different lungs; however, there is no indication as to the number of preparations that will be tested. If you are, in fact, planning to test only one preparation 8 times, this raises concerns in that the measures of variability that you will generate relate to variability of the rat lung and procedures for carrying out the experiment and not the variability of the technical preparation of the formulations. It would be preferable to test multiple formulations as well as using multiple lungs to test each formulation. Also, please state clearly how the data will be generated, i.e., assessing "normal", "lavaged" and "treated" state in turn on each lung *versus* assessing 8 "normal", 8 "lavaged" and 8 "treated" lungs.

6. The protocol states that the experiments will be blinded within surfactant but not across surfactant. It is unclear what the logistic reasons are and what delays will be incurred if the study is blinded across surfactants as well. Because it is important to ensure that all aspects of the experiment are carried out in the same manner for both surfactants and without bias, it is preferable to blind the study across surfactants as well.

7. The protocol appears to place the primary weight of evidence of activity on the excised rat lung experiment with minimal discussion of the bubble surfactometer experiment. If the results of these two methodologies for looking at activity are not consistent in the conclusions that can be drawn, you will need to justify, in your study report, why one methodology rather than the other should be viewed as primary.

8. The definitions of activity provided for the bubble surfactometer experiment appear to focus on the point estimate rather than provide confidence limits for the various definitions provided. In addition, the protocol appears to pre-specify the definition of fully active. As discussed above, the definition of fully active should be based on the activity of original surfactant actually used in the experiment. The definition of equivalent should then describe the limit of activity that could be lost and still be considered equivalent to the original surfactant.

Should you have any questions, please call Ms. Betty Kuzmik, Project Manager, at (301) 827-1051.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-521
HFD-570/Division File
HFD-570/Kuzmik/04-11-97
HFD-570/Schumaker/04-14-97
HFD-570/Himmel/04-16-97
HFD-570/Pina/04-16-97
HFD-570/Nashed/04-11-97
HFD-570/Poochikian/04-14-97
HFD-570/Aras/04-14-97
HFD-570/Wilson/04-16-97
HFD-570/Jenkins/04-16-97
HFD-102/Bilstad/Ripper
HF-53/McCormick (orphan drugs)

4-17-97

R/D BY: BKuzmik/04-07-97
F/T BY: LSlaybaugh/04-17-97

n:\nda\20521\pm\97-04-00.ltr

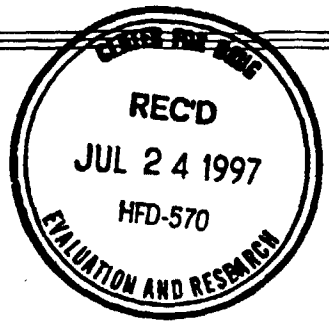
GENERAL CORRESPONDENCE (GC)

4/14/97

**APPEARS THIS WAY
ON ORIGINAL**

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

July 21, 1997



Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
HFD - 001
Food & Drug Administration
5600 Fishers Lane
Rockville MD 20857

RE: Response to Dispute Resolution under 21 CFR §314.103 of July 15, 1997

Product: Infasurf (calfactant)

Dear Doctor Woodcock,

I have carefully read your letter of July 15, 1997 (and the accompanying memoranda by Dr. Jenkins) which declined to adopt ONY's March 14, 1997 request for addressing the scientific/medical dispute of "same drug" status utilizing the mechanism provided by 21 CFR 314.103(b)(3) and instead relied on *ex parte*, in house input. I appreciate your kind words at the end, but must confess that you mistake FDA's total control of the review process for patience on my part.

To be forthright and candid, the reasons in your letter for rejecting our appeal are quite simply wrong. Your letter does not explain why the Agency, despite our repeated importunings, chose not to recruit and utilize outside experts in lung surfactant, which is a highly specialized area, or in neonatology to resolve the scientific dispute. I still do not believe that any knowledgeable, independent experts in lung surfactants and neonatology would endorse the scientific conclusions in your letter. Specifically:

Composition and Activity Differences Between Infasurf and Survanta:

(1) There are qualitative and quantitative differences between Infasurf and Survanta and the Agency's refusal to recognize their existence and significance is scientific error. The decision that quantitative differences between Infasurf and Survanta are irrelevant for differentiating the two drugs is not supported by existing scientific knowledge. The amounts, not the "nature" or the "essence", of substances are what produce biological effects - both beneficial and toxic. The presence of inactive, trace amounts of a substance does not mean there are not qualitative differences. To hypothesize biological activity to components with such minuscule, barely detectable, trace amounts flies in the face of scientific common sense these that there exists a threshold below which components are inactive. The differences in 3 of the 6 components referred to in your letter vary by 200% to 4,000% between the products. Further, these differences are directly related to differences in the nature of the production processes for the two surfactants. The Agency's testing proposal, to prove what is already obvious to independent scientific experts, is impossible to perform. The conclusion of the division (that your letter endorsed) is that, despite these qualitative and quantitative differences, the two products have the same "principal molecular structural features," is incompatible with current scientific knowledge of lung surfactants and could not convince independent experts that it is a valid comparison of these two products.

(2) Your use of "clinical activity" as the only functional analysis that is relevant to determining if the compositional differences are meaningful and significant is also inconsistent with the known pharmacology of surfactants. Extensive data have been provided that the compositional differences between Infasurf and Survanta produce significant differences in biophysical activity, physiologic effects and pharmacologic activity. The requirement that only long term outcome differences, proven in clinical trials (a requirement developed by the Agency after Infasurf's NDA submission), are appropriate for determining whether composi-

tional differences are "relevant" stands opposed to the general practice of using extensive preclinical analysis and testing to develop much of what is known about virtually every pharmacologic agent.

(3) The active moiety of a lung surfactant is the dynamic surface film that it creates. That film is an entity, the "active moiety" of the drug. When important components of the film differ substantially in their components, different active moieties are created. ONY has tried to communicate to the Agency that biophysical and biological testing by recognized methods of a lung surfactant can be sensitive enough to detect differences between two lung surfactant preparations that have significantly different active moieties. When two lung surfactants do have consistent and significant differences in these biophysical and biological test systems they cannot have the same "active moiety."

Clinical Superiority of Infasurf over Survanta

(1) Your letter and Dr. Jenkin's memoranda are inaccurate in their assertion that the physiologic endpoints of FiO2 and MAP (integrated and averaged for the acute phase of the disease, 0-72 hours) are of unknown clinical significance. These endpoints are the objectives of surfactant therapy and are carefully monitored by physicians using surfactants and are the clinicians way of evaluating the severity of RDS is patients. By logistic regression FiO2 and MAP are each, independently, strongly correlated to the outcome of mortality in infants who have RDS. The correlation is statistically significant, ($P < 0.001$) by logistic regression, controlling for birth weight, the other major determinant of mortality in clinical studies of premature infants. This correlation was replicated in the ONY sponsored Exosurf-Infasurf comparison trial for treatment of RDS. The correlation is equally strong and true whether the patients received Survanta, Exosurf or Infasurf. The clinical significance of FiO2 and MAP in RDS is known, and, therefore, your statement is scientifically wrong. Independent, knowledgeable experts would agree these endpoints are clinically significant.

To no neonatologist's surprise, the more severe the acute respiratory failure during the course of RDS, the more likely a premature infant is to die. These associations have been submitted to the reviewing division, but it appears the relationship between severity of RDS and death were not judged to be important during its internal review. These correlations were submitted to you on June 11, 1997 to support the scientific basis for the validity of the subset evaluation of the treatment group of the infants with persistent and severe RDS presented .

(2) Your letter states the Agency's conclusions that the differences between Infasurf and Survanta in the direct clinical comparison trials do not equal "clinical superiority." I believe that physicians who care for neonatal intensive care patients or parents of premature infants with respiratory failure from RDS would have a different opinion. It was an a priori assertion of the Infasurf-Survanta comparison study that it was not designed or intended to determine differences in efficacy outcomes of death or chronic lung disease. FiO2 and MAP, as measures of severity of RDS, were prospectively defined endpoints. The division's review focuses only on methodology of analysis, rather than on whether a study, designed for one purpose, allows insight, if not certainty, of other outcomes. No mention is made in Dr. Jenkins memoranda of insights possible by evaluating the Infasurf-Survanta comparison trials in context of what has been learned from Survanta-Exosurf and Infasurf-Exosurf clinical comparison trials.

Because my principal vocational is that of an academic neonatologist, I have a perspective that focuses narrowly on my own patients and their cohorts and I may lack a wide enough vision of FDA's mission to be able to understand how the Agency, whose primary purpose is to improve the public health, can make a "same drug" decision that is so unfriendly to premature infants. There exists a substantial possibility (acknowledged in your letter) and from my vantage point a certainty, that a significant number of premature infants born between June of 1997 and July of 1998 will have suboptimal outcomes as a result of the general unavailability of Infasurf - and given the Agency's recognition of the safety and efficacy of Infasurf, there is

no possibility of any premature infant benefiting from withholding Infasurf until July 1, 1998, but there is a definite possibility of such infants benefiting if it were available today.

Interpretation of Orphan Drug Regulations

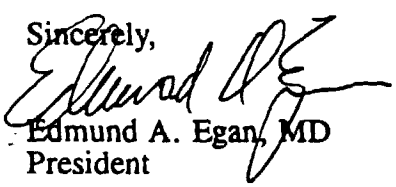
As we stated at the meeting, the Agency's use of this rule is incompatible with the narrow intent of the macromolecular regulations and with the actual differences between both the large and small molecules in Infasurf and Survanta. The Agency first stated Infasurf was "the same" drug as Survanta using 21 CFR 316.3(b)(13)(ii)(D) in a refusal to file letter of May 7, 1995. At a meeting on July 6, 1995 to discuss this decision, it was obvious that the Agency reviewers were scientifically unsophisticated in lung surfactant chemistry, biophysics, physiology and pharmacology when they made this decision. In all the communications since that time, and again in your letter, the attributes of surfactants that make them "closely related", "complex" and "partly definable" have been used in the mistaken justification of this decision.

This regulation was not intended for this purpose, as is stated in your letter, "We agree that the orphan drug regulations do not identify a specific regulatory mechanism for determining the sameness in the case of Infasurf and Survanta." Therefore, I believe the Agency is required to follow the "usual" or small drug methodology because the prologue to the regulations "...regards two drugs as different if they differ with respect to the chemical structure of their active moieties. First, such differences are highly likely to lead to pharmacologic differences. Second, the development of an agent with a novel active moiety is not a financially or intellectually trivial matter; it represents a considerable effort and a substantial risk..."[1]

While I greatly appreciate your professional atmosphere and personal cordiality, as well as that of the Agency's staff at the meeting of June 11, 1997, the failure of the Agency to obtain input and advice from scientists knowledgeable about lung surfactants and neonatology, since the submission of the NDA, has resulted in many FDA decisions during the review being arbitrary and capricious. This has been a systematic problem. For example, Dr. Jenkin's memorandum of April 22, 1997 describes the evolution of the "same" drug issue at a series of meetings attended only by division personnel and supervisory Agency staff, none of whom were experts in lung surfactants. My professional academic career has always involved peer review (as a reviewer and as one being reviewed) of scientific proposals and completed projects. Essential to fairness are reviewers who are unbiased and work within the limits of their expertise. I cannot understand why the Agency has been unwilling to utilize outside consultants to advise it on the "same drug" issue from a scientific and clinical perspective.

The Agency frequently seeks the advice of outside experts, even in areas where it has more staff expertise that it has in lung surfactants and neonatology. It is, indeed, difficult to avoid the conclusion that the Agency, for whatever internal reasons, did not want the enlightenment that independent experts could provide. I again urge the Agency to consult with impartial experts or convene an advisory committee to review this ill informed decision. To fail to do so is to fail in the Agency's essential mission to protect the health of the American people.

Sincerely,



Edmund A. Egan, MD
President

---

1. 56 FR 3341, January 29, 1991.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
ONY, Inc.

DATE OF SUBMISSION
July 21, 1997

ADDRESS *(Number, Street, City, State and ZIP Code)*
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

TELEPHONE NO. *(Include Area Code)*
716-636-9096

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
20-521

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
calfactant	Infasurf

CODE NAME *(If any)*	CHEMICAL NAME
	N/A

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS(S)
Suspension	Intratracheal	35mg/ml

PROPOSED INDICATIONS FOR USE
Prevention of Respiratory Distress Syndrome in premature infants and treatment ("rescue") of newborn infants who develop RDS.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION X other (see page 2)

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

DEC 19 1997

NDA 20-521

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calfactant) Intratracheal Suspension.

Reference is also made to the Agency's letter dated September 26, 1996, the Division's memorandums to Dr. Janet Woodcock dated April 22 and July 2, 1997, and the Agency's letter dated July 15, 1997.

Further reference is made to your submission dated September 24, 1997, in which you submitted a copy of a recent publication which reports the results of a study conducted by Walther, et al. The study by Walther, et al. evaluated the *in vitro* and *in vivo* activity of various modified Survanta preparations, including the addition of exogenous surfactant-associated proteins and peptides to solvent-extracted Survanta. You state in your submission that this study provides further support for your claim that Infasurf and Survanta are "different" drugs with regard to orphan drug exclusivity. You further state that you "believe that the publication of this new study makes the Agency's assumption that SP-B is at active levels in Survanta inconsistent with all the scientific data available."

We have carefully reviewed your September 24, 1997, submission, including the publication by Walther, et al., and we do not agree with your position that these new data are adequate to support a change in the Agency's position that Infasurf should be considered to be the "same" drug as Survanta for purposes of orphan drug exclusivity. As stated in the Agency's letter dated September 26, 1996, if it can be demonstrated that a specific component is present and active in one surfactant and that it is either not present or present at levels that render it inactive in the other surfactant, Infasurf and Survanta may be deemed to be "different." The

results of the study by Walther, et al. suggest that addition of exogenous SP-B to Survanta results in improved oxygenation in adult rats with saline lavage-induced lung injury; however, similar improvements in *in vitro* measurements of surface activity and in situ measurements of lung pressure-volume curves were not observed. The design and analysis of this study do not address the critical question with regard to the determination of whether Infasurf is the "same" drug as Survanta; i.e., are the levels of SP-B present in Survanta active and does the SP-B content contribute to the clinical efficacy demonstrated for Survanta in clinical trials. In this regard, we note your analysis of the Walther, et al. study contained on page 3 of the September 24, 1997, submission in which you conclude that the point at issue for ONY, Inc. - whether SP-B is at inactive levels in Survanta itself - is not explicitly addressed in the manuscript.

If you have any questions, please contact Ms. Betty Kuzmik at (301)827-1051.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-521
HFD-570/Division File
HFD-570/Kuzmik
HFD-570/Schumaker 12/19/97
HFD-570/Pina
HFD-570/Himmel
HFD-570/Nashed
HFD-570/Poochikian

Drafted by: BKuzmik/12-02-97
Reviewed by: MPina/12/2-97; MHimmel/12-2-97; JJenkins/12-3/97;
JBilstad/12-12-97; LDickinson/12-17-97;
CSchumaker/12-18-97
FT: PWilson/12-18-97
WORD
n:\nda\20521\pm\97-12-00.let

GENERAL CORRESPONDENCE (GC)

12/19/97

12/19/97

APPEARS THIS WAY
ON ORIGINAL

Dion Copy

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

May 18, 1995

Charles P. Hoiberg, PhD
Acting Director
Division of Oncology and Pulmonary Drug Products
Office of Drug Evaluation I
Food and Drug Administration
HFD - 150
5600 Fishers Lane
Rockville, MD 20857

RE: INFASURF, NDA 20-521

Dear Dr. Hoiberg:

We are in receipt of your letter of May 10 advising us that under 21 CFR §316.3(b)(13)(ii)(D) you are refusing to file the above referenced NDA.

The reason given in your letter for such an action is that "the Agency has determined that Infasurf and Survanta are the "same drug" as defined by 21 CFR §316.3(b)(13)(ii)(D)."

It is our position that Infasurf and Survanta are not the "same drug." There exists extensive information, including that available in the public domain, that the totally natural surfactant Infasurf (calf lung surfactant extract) is not the same drug as the semi-synthetic surfactant Survanta (beractant). In fact, Infasurf is different from Survanta, just as Survanta is different from Exosurf Neonatal (colfosceril palmitate, cetyl alcohol, tyloxapol), both of which presently have separate Orphan Drug approvals.

In addition we believe that there is no justification for the FDA to refuse to file the Infasurf NDA. The existence of an Orphan Drug approval for a drug does not constitute grounds under §314.101(d) or (e) for refusing to file another NDA during the period of the Orphan Drug's exclusivity. The law provides only that the Agency "may not approve another application *** for such a drug for such disease or condition *** until the expiration of seven years from the date of the approved application***" (emphasis added). Thus, the Infasurf NDA is entitled to be filed and should be reviewed while the "same drug" issue is being considered.

We respectfully request at this time that the Agency proceed with the review of Infasurf. Independently of the NDA review, we request that the Agency schedule a meeting which will provide us the opportunity to discuss the "same drug" issue with the appropriate FDA personnel, including Dr. Robert Temple, Director of the Office of Drug Evaluation I and Dr. Martin Himmel, Supervisory Medical Reviewer, both of whom participated in earlier discussion regarding this product.

Please provide us as soon as possible with available date for a meeting to be held between mid-June and June 30, 1995. We will call you before the end of May to set a definite date and to provide you with the identity of the person who will attend on behalf of ONY and Forest.

Sincerely,

ONY, INC.

for Edmund A. Egan, MD

Edmund A. Egan, MD
President

FOREST LABORATORIES, INC.

for

Michael M. Rosen, PhD
Director of Regulatory Affairs

MAY 10 1995

NDA 20-521

ONY, Inc.
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your March 13, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract).

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit a complete critical medical and technical review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this NDA under 21 CFR 314.101(d) for the following reasons:

> Survanta (a bovine lung surfactant manufactured by Ross Labs) was approved under the Orphan Drug Regulations on July 1, 1991. The Orphan Drug Regulations provide at 21 CFR 316.31 that "After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval..." Based upon information submitted in the NDA for Infasurf, the Agency has determined that Infasurf and Survanta are the "same drug", as defined by 21 CFR 316.3(b)(13)(ii)(D). This provision establishes that "Closely related, complex partly definable drugs with similar therapeutic intent,...would be considered the same unless the subsequent drug was shown to be clinically superior." In order for FDA to approve the NDA for Infasurf before Survanta's exclusivity expires, you must submit data demonstrating that Infasurf is clinically superior to Survanta, as defined by 21 CFR 316.3(b)(3)(i) and (ii).

While not reasons for refusing to file the application, we have the following comments.

1. The release of the subject sterile drug product into interstate commerce by using "parametric release" is unwarranted at this time and would likely result in a Not Approvable recommendation for the NDA. Parametric release has only been approved under very limited circumstances after many years of

successful commercial production history which has not been demonstrated for this NDA. The USP Sterility Test (USP 23 <71>) would be considered an adequate substitute to comply with the regulations under 21 CFR 211.167 (a).

2. We note that a full Environment Assessment (EA) was submitted. As an extract of natural calf lung surfactant, this EA could fall under 21 CFR 25.31a(b)(5) which allows for an abbreviated EA for a substance occurring naturally in the environment. Furthermore, an abbreviated EA would be acceptable under 21 CFR 25.31a(b)(3) since this product has been designated as an orphan drug.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference. If you have any questions please call:

Betty Kuzmik
Consumer Safety Officer
(301) 594-5720

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file this application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, this application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

Under the Prescription Drug User Fee Act of 1992, FDA would normally refund one-half of the fee submitted with an application (25% of the total fee due). Under the provision for Small Business Exception, your fee will be determined one year from the date that this application was submitted. If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

Sincerely yours,

Charles P. Hoiberg, Ph.D.
Acting Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-521
HFD-150/Div. files
HFD-150/Himmel
HFD-150/Pina
HFD-150/Poochikian/5-10-95
HFD-150/Ng
HFD-150/DeGeorge
HFD-150/Choi
HFD-150/Wilson
HFD-150/Koutsoukos
HFD-150/Mehta
HFD-150/Gillespie
HFD-150/Schumaker
HFD-150/Betty Kuzmik
HF-35/Vaccari
GCF-1/Dickinson
HFD-80
DISTRICT OFFICE

drafted: BKuzmik/5-4-95
revised by: CSchumaker/5-4-95 and 5-10; MHimmel/5-5-95; PVaccari/5-8-95; LDickinson/5-8-95
final:

REFUSAL TO FILE (RF)

n:\kuzmikb\n20521.rtf

APPEARS THIS WAY ON ORIGINAL

KUZMICK

NDA 20-521

APR 10 1995

Ony, Inc.
c/o Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Attention: Michael M. Rosen, Ph.D.
Director of Regulatory Affairs

Dear Dr. Rosen:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Infasurf Intratracheal Suspension

Therapeutic Classification: Standard

Date of Application: March 13, 1995

Date of Receipt: March 13, 1995

Our Reference Number: NDA 20-521

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 11, 1995 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Betty Kuzmik
Consumer Safety Officer
Telephone: (301) 594-5720

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

4/10/95

Cathie Schumaker
Chief, Project Management Staff
Pulmonary Drug Products
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-521
HFD-150/Div. Files
HFD-80
HFD-150/Schumaker/4-3-95
HFD-150/CSO/Betty Kuzmik 4/7/95

drafted: kuzmikb/3/28/95
Final typing by:

n:\kuzmikb\n20521.ack

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

March 13 , 1995

Charles P. Hoiberg, Ph.D., Acting Director
Division of Oncology and Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-150
5600 Fishers Place
Rockville, MD 20857

Re: **NDA 20-521/Original New Drug Application**

Product: **Infasurf® (Calf Lung Surfactant Extract) Intratracheal Suspension**

Dear Dr. Hoiberg:
We are submitting an original New Drug Application for Infasurf® (Calf Lung Surfactant Extract) Intratracheal Suspension pursuant to the requirements of section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, 21CFR 314, and supporting Food and Drug Administration guidelines. This submission includes both archival and review copies.

Infasurf® is intended for the prevention and treatment of Respiratory Distress Syndrome (RDS) in neonates. Clinical data is presented for two, randomized, masked, parallel active controlled trials comparing Infasurf® with Exosurf Neonatal®. These studies referred to as the Surfactant Comparison Trial - Prophylaxis (SCT-P) and Surfactant Comparison Trial - Treatment (SCT-T) demonstrate the efficacy and safety of Infasurf® in the prevention and treatment of RDS. The safety has been further demonstrated in open label trials involving over 14,000 infants.

In accordance with our agreement with FDA at the meeting of August 16, 1993 this submission does not contain any case report forms. Hard copies of case report forms and SAS data sets on disks will be provided upon your request. However, this submission does contain death listings from all the clinical trials which can be found in Section 12.

The scope of Section 5: Nonclinical Pharmacology and Toxicology reflects discussions held between Forest-ONY and FDA on February 12, 1992 and March 4, 1992. The decision to limit the kinds of toxicology studies was substantially influenced by the large clinical experience already accumulated. Regarding additional preclinical pharmacology and toxicology requirements, Dr. A. Taylor noted that FDA would be ". . . . flexible on this issue if the benefit of the drug is considered" (FDA meeting minutes of February 12, 1992).

A March 11, 1992 letter to Dr. A. Taylor confirmed a March 4, 1992 telephone conversation between himself and K. Albert, Ph.D. (Forest) in which it was agreed teratology studies would not be required for this NDA. A copy of this letter is included in Section 5.7.

Traditional *in vivo* bioavailability studies of Infasurf® in humans were not done due to the medical fragility of the neonatal population. A request for a waiver of those requirements under 21CFR 320.22(e) is presented in Section 6 and in the clinical pharmacology portion of Section 8.

The information contained in this submission is organized in accord with the Food and Drug Administration Guideline on "Formatting, Assembling and Submitting New Drug and Antibiotic Applications" dated February, 1987. The section numbers are assigned as per Appendix A of that guideline, and the submission is paginated by section. For example, page 08-00123 is page 123 of Section 8: Clinical Data. Once the section is paginated it does not change throughout the submission. Therefore, the Index (Section 1) and Summary (Section 2) maintain the page designation of first use though they appear in each technical section.

The documentation on Sterilization Process Validation is presented per the December 3, 1993 Federal Register. This information has been duplicated from Section 3: Chemistry, Manufacturing and Controls and is formatted as Section 7 per discussion with Dr. Cuny at the Forest/ONY meeting with FDA on November 10, 1993. Section 7 is double paginated in the bottom center of the page and retains the pagination of Section 3 in the lower right corner.

Section 4: Samples, Method Validation and Labeling is extracted from the CMC section. Most of the Section 10: Statistical Data is duplicated from the Clinical section. Four(4) volumes (Vol. 48 through Vol. 51 containing "SAS CATMOD computer output" supporting tables from the 9101P and 9101T studies) were added to the statistical section. Therefore, all of Section 4 and most of Section 10 are double paginated and retain their original pagination in the lower right corner of the page.

As required, a field copy of the Chemistry, Manufacturing and Controls (Section 3), Application Summary (Section 2), application form and certification statement is being submitted to the Buffalo, N.Y. district office.

The applicant received orphan drug designation on June 7, 1985 as shown on page 3-454 of the Orange Book for 1994. (see FDA letter attached).

Additionally this product is a new chemical entity which was not previously been subjected for approval by FDA.

This application is submitted by ONY, Inc. Amherst, N.Y., the sponsor and owner of Infasurf®. Pursuant to the small business administration exception to the Prescription Drug User Fee Act of 1992 (21 U.S.C§ 379h(b)(2)), FDA granted ONY, Inc. a deferral of payment of the application fee for NDA #20-521 in a letter of December 14, 1994. Attached is a copy of that letter.

Samples of this product will be provided upon request.

This application was prepared in cooperation with Forest Laboratories, Inc., NY, N.Y. who has marketing rights to the product as ONY's agent. If you have any questions at any time in your review concerning the material submitted, we would be pleased to discuss them with you by telephone or in person. Please contact Dr. Michael M. Rosen at (212) 421-7850. Correspondence regarding this application should be addressed to:

Michael M. Rosen, Ph.D.
Director of Regulatory Affairs
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Sincerely,
ONY, Inc.

Edmund A. Egan, MD
President

MEMORANDUM

DATE: April 22, 1997

FROM: John K. Jenkins, M.D. 4/24/97
Director, Division of Pulmonary Drug Products, HFD-570

THROUGH: James Bilstad, M.D.
Director, Office of Drug Evaluation II, HFD-102 4/29/97

TO: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research, HFD-1

Murray Lumpkin, M.D.
Deputy Director (Review Management), Center for Drug Evaluation and Research, HFD-2

SUBJECT: NDA 20-521 Request for Dispute Resolution under 21 CFR 314.103

On March 14, 1997 ONY Inc., the sponsor of NDA 20-521 for Infasurf (calf lung surfactant extract), submitted a request for dispute resolution to the Office of the Center Director. The issues in question are whether Infasurf is the "same drug" as Survanta (beractant) and whether Infasurf is clinically superior to Survanta. The purpose of this memorandum is to provide the Division of Pulmonary Drug Products' perspective on the complex scientific and regulatory issues related to the Center's determination that Infasurf and Survanta are the "same drug" under the orphan drug regulations and that clinical superiority has not been adequately demonstrated.

BACKGROUND

Survanta Approval and Orphan Drug Exclusivity

NDA 20-032 for Survanta[1] was approved in 1991 for the "prevention and treatment ("rescue") of

[1] The DESCRIPTION section of the Survanta package insert states: SURVANTA® (beractant) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitolyphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. Its protein content consists of two hydrophobic, low molecular weight, surfactant associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A. Each mL of SURVANTA contains 25 mg/mL of phospholipids. It is an off-white to light brown liquid supplied in single-use glass vials containing 8 mL (200 mg phospholipids).

Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants." Survanta was granted 7 years of marketing exclusivity under the orphan drug regulations; the period of exclusivity expires on July 1, 1998.

Regulatory History of NDA 20-521 (see the attached Administrative Review of and NDA 20-521)

ONY Inc. originally submitted NDA 20-521 for Infasurf on May 13, 1995. During the initial filing review, the issue of Survanta's orphan drug exclusivity was raised and a review was conducted to determine if Infasurf was the "same" or "different" from Survanta based on the orphan drug regulations. The Division and Office concluded that the two surfactants were the "same drug" under the orphan drug regulations (see below for the scientific and regulatory rationale for this decision). An overview of the clinical trials submitted in the original application revealed no studies that could support an evaluation of possible clinical superiority of Infasurf over Survanta. Following further consultations with Dr. Bilstad, Ms. Dickinson from the Office of General Counsel, and Dr. McCormick from the Office of Orphan Drug Products, the Division issued a Refuse to File (RTF) letter for this application on May 10, 1995[2].

ONY expressed their disagreement with the Division's decision and immediately requested a meeting to discuss this issue. At the July 6, 1995, meeting, ONY's legal counsel, Mr. Kaplan, argued that the RTF action was inappropriate and that the application should be filed and reviewed based on the original submission date. Dr. Egan, President of ONY, along with several consultants, argued that Infasurf and Survanta were not the same drug for several reasons, including: 1) Infasurf is prepared as an extract of calf whole lung lavage while Survanta is prepared as an extract of minced bovine lung; 2) Ross, the manufacturer of Survanta

while ONY does not add any substances to Infasurf; and 3) the levels of SP-B in Survanta are very low and sub-threshold for activity while the levels of SP-B in Infasurf are 20-40 times higher and necessary for Infasurf activity. ONY presented data from the published literature and from their own work, including new preliminary data on comparative SP-B levels in the two products generated after the RTF letter was issued, in support of their

---

[2] The stated reason for the RTF action was: "We are refusing to file this NDA under 21 CFR 314.10(d) for the following reasons: Survanta (a bovine lung surfactant manufactured by Ross Labs) was approved under the Orphan Drug Regulations on July 1, 1991. The Orphan Drug Regulations provide at 21 CFR 316.31 that "After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which the orphan drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before expiration of seven years from the date of such approval..." Based upon information submitted in the NDA for Infasurf, the Agency has determined that Infasurf and Survanta are the "same drug", as defined by 21 CFR 316.3(b)(13)(ii)(D). This provision established that "Closely related, complex partly definable drugs with similar therapeutic intent,...would be considered the same unless the subsequent drug was shown to be clinically superior." In order for FDA to approve the NDA for Infasurf before Survanta's exclusivity expires, you must submit data demonstrating that Infasurf is clinically superior to Survanta, as defined by 21 CFR 3.16.3(b)(3)(I) and (ii)."

claim of the pivotal role of SP-B in normal surfactant function. Dr. Egan and the ONY consultants expressed their strong personal belief that Infasurf was clinically superior to Survanta and stated that they had completed a clinical trial comparing the two. The data from the trial were not included in the original NDA; however, ONY promised that the final study report would be submitted to the Division for review by mid-July 1995.

The Division, in consultation with Drs. Bilstad and Temple, Ms. Dickinson, and Dr. McCormick, agreed that ONY had presented a credible scientific argument for why Infasurf and Survanta should be considered "different drugs" and that the NDA would be filed for review if ONY submitted the data supporting the pivotal role of SP-B along with data demonstrating the marked differences in SP-B levels between the two surfactants. The "same" versus "different" issue would then become a review issue and would be based on the SP-B argument or the Infasurf versus Survanta comparison trial which the sponsor claimed would demonstrate that Infasurf was clinically superior to Survanta. It was agreed, however, that the RTF action for the original application was correct since the data addressing the "same" versus "different" drug issue (i.e., the SP-B data presented at the July 6, 1995, meeting and the Infasurf versus Survanta trial) were not contained in the original application and were necessary for review.[3]

On July 13, 1995, the Division issued a letter to ONY stating its willingness to file a resubmitted application[4]. ONY resubmitted the application on July 27, 1995, and in the cover letter stated

---

[3] At a subsequent meeting of the Center's Refuse to File Review Committee, the Committee concluded that an RTF action is not appropriate in situations where the product that is the subject of the NDA is blocked from marketing due to exclusivity granted to another product. The rationale was that the Center could complete the review of the application and if all other regulatory requirements for approval were met, could issue an action letter with final approval delayed pending expiration of the exclusivity. The Office of General Counsel subsequently issued a written opinion that confirmed the Committee's conclusion that an RTF action is not appropriate in the above described situation. The Office of General Counsel also subsequently issued a written opinion supporting the Center's ability to issue a "Tentative Approval" action, similar to the mechanism utilized by the Office of Generic Drugs, in cases where all regulatory requirements for approval of an NDA have been meet by the sponsor and the only block to final approval is expiration of the period of exclusivity for the competing product.

[4] The conditions listed in the letter were: "The new information that was presented at the meeting provides a theoretically valid argument that Infasurf is different from Survanta. We are willing to file your NDA if the following are included in your resubmission: 1) The data which were presented at the meeting and which support the contribution of SPB to the effect of Infasurf must be submitted in a manner consistent with an NDA submission; 2) Commit to provide comparative CMC data from an FDA-inspected laboratory for the analysis of SPB in Survanta and Infasurf by no later than 4 months after the NDA is resubmitted. Appropriately validated methods should be used to generate the requested comparative data on 4 to 6 batches of each product. The data should include the batch number and expiration of the batch tested and the date the analysis was performed. If the determination is made that Infasurf is different from Survanta based on the above comparative data, appropriate regulatory specifications must be set for various components in Infasurf including SPB. Since SPB was not specifically assayed in the clinical lots, you must propose a plan for linking the clinical lots with the to-be-marketed lots with regard to concentration of SPB. The application will be considered resubmitted when we have received the data requested in #1 above."

their commitment to provide validated comparative data for SP-B for the two surfactants by December 1, 1995. The application was filed by the Division with the resubmission date as the date for calculation of the User Fee Goal Date.

Further internal discussions of the "same" versus "different" drug issue occurred in a meeting on March 4, 1996, which included Drs. Temple, Botstein, Bilstad, and McCormick in addition to representatives from the Division. The participants at the meeting agreed that the available data on Infasurf and Survanta did not support a conclusion that they were "different" drugs under the orphan drug regulations. It was agreed that the SP-B data that ONY had promised to generate (and which had not yet been submitted) were critical to ONY's argument. It was further agreed that if both surfactants were shown to contain SP-B, albeit at different levels, it might be necessary for ONY to provide data demonstrating the significance of the differences in SP-B levels with regard to activity of the surfactants. At a subsequent meeting, similar conclusions were reached with regard to Curosurf, a porcine derived surfactant under development by Dey Laboratories. ONY was informed of these conclusions at a meeting held on March 20, 1996, to discuss orphan drug and CMC issues related to NDA 20-521. In that meeting, ONY and its consultants expressed surprise that this "new" requirement was being requested since they had felt that the orphan drug issue was resolved with their agreement at the July 6, 1995, meeting to provide a validated comparative assay of SP-B levels in the two surfactants. The Division made clear to ONY at the March 20, 1996, meeting that the "same" versus "different" drug issue was a review issue and that a final decision had not yet been made (again the comparative data for SP-B levels in the two surfactants had not yet been submitted by ONY). ONY was also informed that the issue was scheduled to be discussed at a Center level meeting in the near future and that they would be informed promptly of the results of that meeting.

Center level discussions of the orphan drug issues related to NDA 20-521 occurred at an April 24, 1996, meeting attended by Drs. Woodcock, Lumpkin, Temple, Bilstad, McCormick, Ms. Dickinson, Ms. Axelrad, Mr. Hare, and Division representatives. The participants concurred with the Division/Office assessment that Infasurf and Survanta were the "same" drugs under the orphan drug regulations.[5]

Dr. Egan was informed of these Center level decisions in a telephone conversation held on April

---

[5] The conclusions from the meeting minutes were: "1.Survanta, Infasurf and Curosurf are the "same" drug under the Orphan Drug Regulations. To prove that Infasurf is different from Survanta the sponsor must provide quantification of SPB and proof that the level of SPB in Survanta is inactive. The same approach would apply to Curosurf; 2) Dr. Jenkins will notify ONY and Dey Labs of these Center level determinations. The Commissioner's Office will be notified by Dr. Lumpkin of this issue; 3) The Division will not refuse to file the Curosurf NDA. A consult will be sent to GC requesting a legal opinion regarding the issue of whether a RTF action can be taken on the basis of a drug being blocked by Orphan Drug Exclusivity; 4) GC will be consulted regarding the ability of CDER to issue a "tentative" approval letter to NDAs similar to that issued to ANDAs by OGD if the only blockage to approval is exclusivity issues; 5) The therapeutic equivalence code for Survanta, Infasurf and Curosurf will be the same once approved, however, they will be listed as not interchangeable."